UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
[illegible]	[illegible]	[illegible]	[illegible]

EXAMINER

HN22/0213

ARLES A TAYLOR JR
JENKINS & WILSON P A
SUITE 1400 UNIVERSITY TOWER
3100 TOWER BOULEVARD
DURHAM NC 27707

ART UNIT	PAPER NUMBER
[illegible]	5

1651

DATE MAILED: 03/13/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/527,352	Applicant(s) LeCruse et al.
	Examiner Vera Afremova	Group Art Unit 1651

X Responsive to communication(s) filed on *Jun 19, 2000* .

This action is **FINAL**.

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

X Claim(s) *1-64* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

X Claim(s) *1-64* is/are rejected.

Claim(s) _____ is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is approved disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been

received.

received in Application No. (Series Code/Serial Number) _____ .

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

X Notice of References Cited, PTO-892

X Information Disclosure Statement(s), PTO-1449, Paper No(s). *4*

Interview Summary, PTO-413

X Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 1-64 are pending.

Claim Rejections - 35 U.S.C. § 112

Claims 12, 24, 39-64 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12, 24, 39 and 52 are rendered indefinite by the phrase "calculating a biliary clearance value" because this phrase as claimed fails to particularly point out and distinctly claim the subject matter which applicants regard as the invention since the metes and bounds of the claims can not be determined as claimed. It is suggested to insert specific phrase related to particular calculation as intended by applicants or as disclosed in the specification at page 19, lines 20-24, for example.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-11, 13-23 and 25-38 are rejected under 35 U.S.C. 102(b) as being anticipated by LeCluyse et al. [U] or Liu et al [IDS-EE].

The claims are directed to a method of screening a candidate compound or a plurality of candidate compounds for susceptibility to biliary excretion wherein the method comprises step of providing a sandwich culture of hepatocytes with one bile canaliculus or with a canalicular network, step of exposing candidate compound(s) to the sandwich culture and step of determining amount of the candidate compound(s) in the bile canaliculus or within the canalicular network. Some claims are drawn to the method of screening comprising additional step of washing the culture and using candidate compound with radiolabeled or fluorescent marker. Some claims are further drawn to the use of rat hepatocytes, to the use of long-term hepatocyte culture, to the use of collagen for the sandwich culture matrix in the method of screening candidate compounds.

LeCluyse et al. [U] disclose a method of screening candidate compounds such as carboxyfluorescin (CF) and/or rhodaminephaloidin for susceptibility to biliary excretion wherein the method comprises step of providing collagen-sandwich culture of rat hepatocytes with network of bili canaliculi, step of exposing the compound to the sandwich culture and step of determining amount of the compound within canalicular network or monitoring excretion of CF by fluorescent microscopy (see abstract or see page C1769, col.2, par. 2). The cultures were maintained for at least 4 days and more. The disclosed method also encompasses step of washing the culture with EDTA.

Liu et al [IDS-EE] disclose a method of screening a plurality of candidate compounds such as taurocholate, radiolabeled enkephalin, alanine, morphine, inulin, etc. for susceptibility to biliary excretion wherein the method comprises step of providing collagen sandwich culture of rat

hepatocytes with extensive bile canaliculi, step of exposing the candidate compounds to the sandwich culture and step of determining amounts of the candidate compounds in the canalicular network. The cited reference particularly teaches the effective use of the in vitro sandwich-cultured hepatocytes for investigating biliary excretion of drug candidates.

The cited method for screening candidate compounds clearly anticipate the claimed invention because they comprise identical active steps and identical structural elements as claimed.

Claims 1-64 are rejected under 35 U.S.C. 102(a) as being anticipated by Liu et al. [IDS-CC].

The claims 1-11, 13-23 and 25-38 as explained above. Some claims are/are further drawn to additional step of determining or calculating a biliary clearance value for candidate compound. Some claims are drawn to additional steps of washing and/or lysing the culture and to determining amounts of metabolite of the parent candidate compound exposed to the culture.

Liu et al. [IDS-CC] disclose a method of screening various candidate compounds including radiolabeled and fluorescent compounds such as taurocholate, enkephalin, inulin, etc. for susceptibility to biliary excretion wherein the method comprises step of providing collagen sandwich culture of rat hepatocytes with extensive bile canaliculi, step of exposing the candidate compounds to the sandwich culture and step of determining amounts of the candidate compounds in the canalicular network. The cited reference also discloses step of determining the *in vitro* biliary clearance value and teaches that the *in vitro* biliary clearance value corresponds to the *in*

vivo biliary clearance. The cited method of screening candidate compounds also encompasses steps washing and/or lysing the culture of hepatocytes by teaching evaluation of uptake or accumulation of compounds in intact or disrupted canaliculi exposed to standard buffer or Ca2+free buffer respectively. And the cited method encompasses screening of parent compounds and metabolite of parent compounds by teaching excretion of carboxydichlorofluorescein (CF) which is a metabolite of parent compound carboxyfluorescein diacetate (CFDA).

Thus, the cited reference anticipates all active steps and structural elements of the presently claimed invention.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over LeCluyse et al. [U] or/and Liu et al [IDS-EE] taken US 5,602,026 [A], Liu et al. [IDS-DD] and Poole et al. [U].

The claims are directed to a method of screening candidate compound for susceptibility to biliary excretion in a sandwich culture of hepatocytes by determining amount of the candidate compound in bili canaliculi or canalicular network. Some claims are further drawn to the use of

various hepatocytes such as rat or human hepatocytes. Some claims are/are further drawn to additional step of determining or calculating a biliary clearance value for candidate compound.

The cited references LeCluyse et al. [U] or/and Liu et al [IDS-EE] are relied upon as explained above. They appear to lack disclosure or suggestion with regard to the use of hepatocyte sandwich cultures with other hepatocytes than rat derived hepatocytes.

US 5,602,026 [A] is relied upon for the disclosure of culturing or maintaining rat and human hepatocytes in sandwich configuration with bili canalicular network (col. 7, lines 65-67). The cited patent teaches that the sandwich culture of hepatocytes has metabolic function of the liver in vivo (col.8, line 23) and that the sandwich culture is suitable for studying hepatocyte metabolism and recovering product of hepatocyte metabolism (col. 8, line 33). In addition, the cited patent suggests various extracellular matrix components (col. 8, lines 38-41).

The primary references LeCluyse et al. [U] and Liu et al [IDS-EE] appear to lack the particular disclosure related to determining a specific value such as "biliary clearance value" for candidate compound released into bili canaliculi.

The secondary reference by Liu et al. [IDS-DD] discloses method of screening candidate compound taurocholate (TC) for susceptibility to biliary excretion in sandwich culture of hepatocytes and suggests determining Km and Vmax values for examining activity and regulation of hepatobiliary transport systems.

The secondary reference by Poole et al. [U] discloses method of screening candidate compound thyroxine T4 for susceptibility to biliary excretion *in vivo* and in the culture of

hepatocytes and teaches direct correlation for the *in vivo* biliary clearance value for thyroxine and the *in vitro* accumulation of thyroxine.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to modify the methods of screening candidate compounds for susceptibility to biliary excretion of the primary references [U] and [IDS-EE] by determining the values related to biliary excretion of candidate compounds as suggested by the secondary references [IDS-DD] and [U] with a reasonable expectation of success in investigating susceptibility of candidate compound or drug interaction relevant to biliary excretion because the sandwich culture of hepatocytes is known to have metabolic functions of the liver *in vivo* and several various and specific parameters have been suggested in the prior art for evaluation and comparison of biliary clearance or biliary excretion of test compounds the *in vitro* and the *in vivo* systems.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 U.S.C. § 103.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (703) 308-9351. The examiner can normally be reached on Monday to Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn, can be reached on (703) 308-4743. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vera Afremova,

Art Unit 1651

march 8, 2001.

SANDRA E. SAUCIER
PRIMARY EXAMINER